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Thoracic Esophageal Carcinoma Above the Carina: A More Formidable Adversary?

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Background: Prognosis with esophageal carcinoma above the carina is generally thought to be the worst without any conclusive demonstration.
Methods: Clinicopathologic features of 101 patients with thoracic esophageal carcinoma above the carina (AC group) were compared with those of 665 patients with a tumor below this level (BC group).
Results: The number of T4 tumor was significantly larger in the AC group ($P < 0.001$). Survival curve for all patients in the AC group was significantly worse than the BC group ($P < 0.001$). Survival in patients who underwent any treatment other than esophagectomy was equally bad in the two groups. However, survival in patients undergoing esophagectomy was similar in the two groups ($P = 0.64$), with the cumulative 5-year survival rates of 44.5% and 43.1%, respectively. Even in patients with metastatic disease in the lymph nodes, the cumulative 5-year survival rates after radical esophagectomy were similar.
Conclusions: The prognosis of patients in the AC group is generally worse than the BC group because of the close anatomical relationship with the tracheobronchial tree. However, radical esophagectomy is recommended for patients at stages less advanced than T4.
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KEY WORDS: **esophageal carcinoma; tracheal bifurcation; tracheobronchial tree; esophagectomy; lymph node metastasis; survival rate**

INTRODUCTION

The results of treatment for esophageal carcinoma are generally unsatisfactory, and the prognosis of tumors in the upper thoracic esophagus is considered to be the worst. Long-term results after any treatment except surgery are very poor. Moreover, many surgeons who treat esophageal carcinoma do not expect to cure the disease by operation. Thus reports of survival after surgical treatment, especially from western countries, rarely include the results of carcinomas of the upper thoracic esophagus [1–4]. The reason for the poor results of treatments for carcinoma in the upper thoracic esophagus may be the anatomical position in the upper mediastinum. However, reports with formal consideration of these factors have not been published, nor have the characteristics of the disease been described in detail in the literature.

Because the esophagus is divided into various segments in the literature, any combined analysis of the frequency of carcinoma by site can be no more than a crude estimate. The 1987 TNM classification [5] defined the upper thoracic esophagus as that portion from the thoracic inlet to the level of the tracheal bifurcation. A similar anatomical classification had been proposed in 1976 by the Japanese Society for Esophageal Diseases [6]. According to the Report of Treatment Results of Esophageal Carcinoma in Japan [7], carcinoma in the

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upper thoracic esophagus affected 10% (481) of 4,691 registered patients with thoracic esophageal carcinoma in Japan. Reports of questionnaires from Japan using the Japanese definition showed the worst results after esophagectomy for carcinoma in the upper thoracic esophagus [7,8].

Many surgeons who responded to this questionnaire may have never given up their attempts to cure the disease by surgery. We have been trying to cure the disease in our institution for three decades. This report describes our experience over the last 10 years of treatment of thoracic esophageal carcinoma above the tracheal bifurcation (carina) and discusses the outcome in order to clarify the characteristics of the disease.

MATERIALS AND METHODS

From 1985 through 1994, we treated a total of 766 patients with thoracic esophageal carcinoma. Of these, 101 had a tumor in the upper thoracic esophagus and 665 a tumor in the middle or lower esophagus. Their characteristics and outcome were compared. Plain chest X-ray, esophagogram, computed tomography scanning, esophagoscopy, cervical and abdominal ultrasonography, and endoscopic ultrasonography were used for the routine evaluation of tumor stage. Bronchoscopy, magnetic resonance imaging, or gallium scanning were used when appropriate. Tumor sizes before treatment were measured on esophagography X-ray films. The location of tumor and position of the tracheal bifurcation were also judged by esophagography. Among these 766 patients, 489 underwent esophagectomy leaving no residual tumor (R0 esophagectomy according to the R classification of the TNM classification) [5]. Of these 489 patients, 37 had a tumor above the tracheal bifurcation. Their characteristics and outcome were compared with those of 452 patients who had a tumor below the carina and who underwent R0 esophagectomy.

A total of 254 patients underwent cervical, mediastinal, and abdominal lymph node dissection (3-field dissection) in addition to esophagectomy [9]. Of the 254 patients, 41 had a tumor above the carina and 213 below. Seventeen patients who underwent esophagectomy with residual tumor (R1 esophagectomy) were included in this group of 41.

Sixty-seven patients with tumor above the carina underwent R0, R1, or R2 esophagectomy, among whom four had radiotherapy, two chemotherapy, and two chemotherapy followed by radiotherapy before surgery. After surgery, 26 patients received radiotherapy (48–84 Gy) including 16 for residual tumor, and eight underwent chemotherapy (three with cisplatin, four tegafur, and one bleomycin), of whom four received chemoradiotherapy.

The site of the tumor was taken as the approximate center of the lesion on the esophagography X-ray film. The stage and anatomical subsite of the lesion and the presence or absence of residual tumor after esophagectomy were expressed using the 1987 TNM classification [5]. The International Histological Classification of the World Health Organization [10] was used for histological typing of the esophageal tumors. Follow-up information was obtained in December 1994 from the patients' records and the family register. Differences in distribution of factors were compared using the Chi-square test. The life table method of Cutler and Ederar [11] was used to estimate survival rates, and all deaths were included. The log-rank test and the generalized Wilcoxon test [12] were used to compare differences between two survival curves. Survival curves were computed using the method of Kaplan and Meier [13].

RESULTS

The characteristics of all patients with tumors above and below the tracheal bifurcation are shown in Table I. Among 101 patients in the AC group, the proportion of female patients was significantly smaller ($P = 0.0246$), and that of T4 tumors was significantly larger ($P < 0.009$), whereas the mean age, length of history of the tumor, mean tumor size, N factor, M factor, comprehensive TNM stage, and histology of the tumor were similar in the two groups.

The T4 tumors above the carina involved the tracheobronchial tree in 27 patients (26.7% of AC group), five of them simultaneously invaded the aorta (5.0% of AC group), whereas the T4 tumors below the carina invaded the tracheobronchial tree in 34 patients (5.1% of BC group), the aorta in 21 (3.2%), the lung in 11 (1.7%), the pericardium in five (0.8%), and the diaphragm in one, and other six tumors invaded the abdominal organs such as the liver and pancreas. The proportion of T4 tumors involving the tracheobronchial tree in the AC group was significantly higher ($P < 0.001$). Among the 101 patients in the AC group, four at stage T4 underwent radiotherapy first; tumors were then judged to be resectable and they preceded to esophagectomy. Two other patients with T4 tumors first underwent chemotherapy with cisplatin (80 mg/m^2) and 5-fluorouracil (5-FU) (800 mg/m^2 for 5 days), one of whom required an emergency esophagectomy for tumor perforation. The other underwent esophagectomy for regrowth of tumor after several months of complete response to the chemotherapy.

Of the 101 patients in the AC group, 67 (66.3%) underwent esophagectomy, and 551 (82.9%) of 665 patients in the BC group. Resectability of the tumor was significantly less in the AC group ($P < 0.001$). Mean survival after the first treatment for all patients in the AC group was 528 ± 667 days, which was significantly shorter than that for patients in the BC group (797 ± 803 days) ($P < 0.001$). The cumulative 5-year survival rates

TABLE I. Characteristics of All Patients With Thoracic Esophageal Carcinoma Above or Below the Carina

Characteristics	Tumor location: GROUP AC (above the carina) (n = 101)	Tumor location: GROUP BC (below the carina) (n = 665)	*P* value
Age (yr)[a]	62.3 ± 9.3	62.8 ± 9.9	0.3359
Sex (male/female)	97/4	585/80	0.0246
History (months)	2.3 ± 2.7	2.3 ± 3.0	0.4124
Tumor size (cm)	6.6 ± 3.2	6.1 ± 3.7	0.6982
TNM classification			
Tis/T1/T2/T3/T4/TX	4/18/9/42/27/1	33/182/107/257/78/8	$P < 0.05$
N0/N1/NX	42/58/1	312/337/16	NS
M0/M1/MX	73/28/0	512/145/8	NS
Stage 0/I/IIA/IIB/III/IV/X	4/15/11/5/38/28/0	33/139/113/44/181/145/10	NS
Histology			
Squamous cell carcinoma	96	587	0.0614
Adenocarcinoma	1	17	
Adenosquamous carcinoma	1	11	
Undifferentiated carcinoma[b]	0	15	
Carcinosarcoma	0	15	
Malignant melanoma	0	2	
Adenoid cystic carcinoma	0	1	
Others	3	17	

[a]Values are mean ± sd.
[b]Including small cell carcinoma.
NS: not significant.

after the main treatment for the patients in the AC and BC groups were 18.3% and 35.0%, respectively. The two survival curves were significantly different ($P < 0.001$) (Fig. 1). After excluding the female patients, the difference in survival between the two groups was still significant ($P < 0.001$).

Among the 101 patients in the AC group, 37 (36.6%) underwent R0 esophagectomy, whereas 452 (68.0%) of the 665 patients in the BC group were able to undergo a similar procedure. The patients who underwent R0 esophagectomy was significantly smaller in the AC group ($P < 0.001$). Characteristics of the 37 patients in the AC group and of the 452 in the BC group were compared in those patients who underwent R0 esophagectomy (Table II). Stage distributions of the tumors in the two groups were similar. The patients at pT4 in the AC group were treated with combined resection of the involved trachea or thyroid, whereas those in the BC group underwent resection of the invaded trachea, bronchus, pericardium, diaphragm, or liver. The duration of the operation, the operative complication rates, and the operative mortality rates in the two groups were similar. However, the patients in the AC group were significantly younger ($P = 0.0258$), and there was significantly larger operative blood loss. The recurrent laryngeal nerves run just beside the esophagus in the upper mediastinum and the neck, and recurrent nerve palsy caused by surgery occurred more frequently in the AC group than in the BC group (29.7% and 18.6%), although the difference was not statistically significant ($P = 0.1523$). Pathologic examination of the resected specimens showed that the mean tumor size, mean numbers of nodes dissected, and those with metastasis were similar, even though the proximal margin of tumors above the carina was significantly shorter. Mean survival was not significantly different between these two groups. Cumulative 3- and 5-year survival rates after esophagectomy for the patients in the AC group were both 44.5%, and those for patients in the BC group were 54.8% and 43.1%, respectively. The two survival curves did not differ significantly ($P = 0.64$) (Fig. 2).

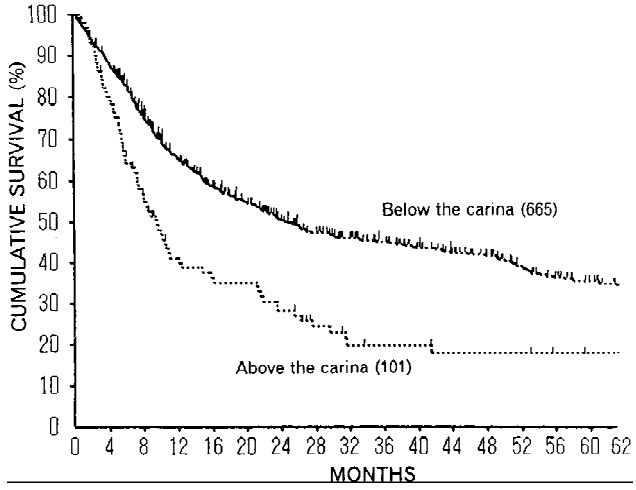

Fig. 1. Survival curves from time of initial treatment for patients with thoracic esophageal carcinoma above and below the tracheal bifurcation (carina).

TABLE II. Characteristics of Patients With Thoracic Esophageal Carcinoma Above and Below the Carina and Who Underwent Esophagectomy Without Residual Tumor (R0)

Characteristics	Tumor location: GROUP AC (above the carina) (n = 37)	Tumor location: GROUP BC (below the carina) (n = 452)	*P* value
Age (yr)[a]	60.2 ± 7.2	62.7 ± 9.6	0.0258
pTNM classification			
pTis/T1/T2/T3/T4/TX	3/13/3/15/3/0	14/143/71/206/14/4	NS
pN0/N1/NX	18/19/0	179/273/0	NS
pM0/M1(LYM)/MX	29/8/0	372/80/0	NS
pStage 0/I/IIA/IIB/III/IV/X	3/9/6/5/7/7/0	14/90/68/74/117/86/3	NS
Duration of operation (min)[a]	484.5 ± 125.8	458.3 ± 93.7	0.1111
Operative blood loss (ml)[a]	808.1 ± 483.2	597.9 ± 378.7	0.0069
Complications (with/without)	23/14	239/213	0.3589
Operative deaths	2 (5.4%)	30 (6.6%)	0.9566
Tumor size (cm)[a,b]	4.7 ± 3.1	4.9 ± 2.9	0.3563
Proximal margin (cm)[a,b]	2.4 ± 2.3	5.1 ± 3.0	$P < 0.1^{-6}$
No. of lymph nodes[a,b]			
Dissected	60.5 ± 29.5	54.8 ± 27.4	0.1133
Positive	2.9 ± 5.0	3.0 ± 5.6	0.4526
Survival (days)[a]	937.9 ± 881.4	967.7 ± 852.1	0.4191

[a]Values are mean ± sd.
[b]In the resected specimen.
NS: not significant.

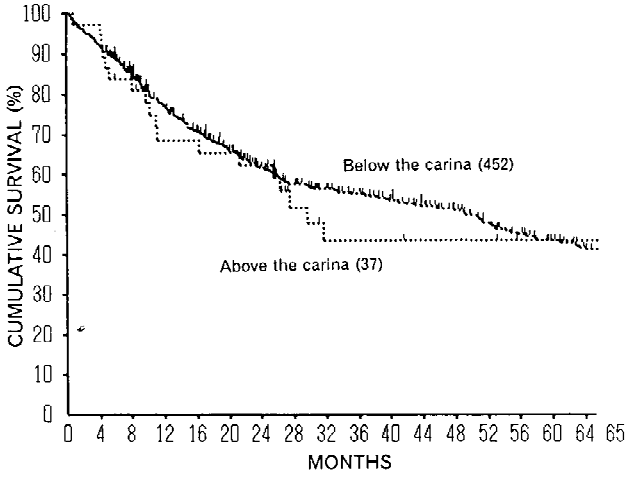

Fig. 2. Postoperative survival curves for patients with thoracic esophageal carcinoma above and below the tracheal bifurcation (carina) who underwent esophagectomy without residual tumor.

Cumulative 3- and 5-year survival rates in the 30 patients who underwent incomplete resection of the tumor (R1 or R2 esophagectomy) above the carina were 7.7% and 3.8%, respectively, the comparable rates in the 85 patients who had incomplete resection of tumors below the carina being 18.3% and 14.5%, respectively. The two survival curves were not statistically significantly different ($P = 0.9282$).

Among 41 patients who underwent 3-field dissection in the AC group, 15 (36.6%) were found histologically to have metastasis in the cervical lymph nodes, and 22 (53.7%) in the mediastinum, whereas only 4 patients (9.8%) had metastasis in the abdominal lymph nodes, of whom all had 11 positive nodes in the resected specimen. Among 213 patients who underwent 3-field dissection in the BC group, 48 (22.5%) were found histologically to have metastasis in the dissected cervical lymph nodes. Although the difference between these two groups in the rate of metastasis to the cervical and mediastinal lymph nodes was not significant ($P = 0.0872$ and $P = 0.8173$), the rate of metastasis to the abdominal lymph nodes was significantly lower in the AC group ($P < 0.001$).

The cumulative 5-year survival rates after 3-field dissection for the patients with lymph node metastasis in the neck or mediastinum in the AC group were 30.7% and 30.6%, respectively. Two of the four patients with abdominal lymph node metastasis in the resected specimen in the AC group are still alive 1 or 2 years after surgery. For patients who had lymph node metastasis in the neck, mediastinum, or abdomen in the BC group, 5-year survivals were 29.4%, 34.2%, and 28.1%, respectively.

Four patients in the AC group underwent postoperative chemotherapy using cisplatin plus 5-FU, tegafur, or bleomycin, and all of these died of the disease within 4 years of surgery. Twenty-two patients received 50–80 Gy of radiotherapy after surgery, 15 for residual tumor, 7 for prophylactic intent. Among these, only two patients (9%) are alive >5 years and both received prophylactic irradiation. Four patients underwent chemoradiation with tegafur (three patients) and cisplatin plus 5-FU (one pa-

tient) combined with 50 Gy of irradiation. Two of them are alive after 93 and 26 months, and one died of unrelated disease 65 months after surgery.

The principal treatment in our institute for patients with T4 esophageal tumors unsuitable for surgical treatment was chemotherapy using cisplatin and 5-FU followed by external beam irradiation. Other treatments were decided individually according to the patients' condition or their own selection. Among 101 patients in the AC group, 34 underwent nonsurgical treatments because of the extent of the T4 tumor or accompanying other serious diseases. Nine patients underwent radiotherapy alone, eight chemotherapy alone, and 13 had both. The cumulative 3-year survival rates for patients who underwent radiotherapy alone, chemotherapy alone, and both treatments combined were 3.5%, 4.8%, 7.7%, respectively. Among the 125 patients who underwent nonsurgical treatments in the BC group, 28 received radiotherapy alone, 29 chemotherapy alone, and 26 both treatments. Their cumulative 3-year survival rates were 9.8%, 5.8%, and 6.9%, respectively. Survival curves for patients in the two groups undergoing nonsurgical treatments were not significantly different (radiation: $P > 0.1$; chemotherapy: $P = 0.189$; chemoradiation: $P = 0.717$).

DISCUSSION

This survey confirms the generally held view that survival of patients with a thoracic esophageal carcinoma above the carina is worse than in those with a carcinoma at other sites of the thoracic esophagus. Although the mean tumor size on the esophagogram was not larger for tumors above the carina, the proportion of patients with T4 tumors was significantly higher. The percentage of tumors involving organs that are hazardous to excise, such as the tracheobronchial tree, was larger in the patients with a tumor above the carina. Combined resection of the tracheobronchial tree was generally considered too invasive and therapeutically not worthwhile, although there are benefits in resection of the lung, pericardium, or diaphragm [2,14]. The lower resectability rate of tumors above the carina is attributable to the anatomical position of the esophagus, especially in relation to the tracheobronchial tree, because the proportion of tumors invading this organ was higher in tumors above the carina, although the proportion with a tumor invading other organs except the tracheobronchial tree was similar or rather smaller. These results justify the classification of anatomical subsite in the TNM classification and the classification of the site of the lesion by the Japanese Society for Esophageal Disease as the upper thoracic esophagus.

In those patients who underwent curative esophagectomy, survivals for patients with tumors above and below the carina were similar. The most background factors were similar, although mean operative blood loss was larger and mean age younger in the AC group. Postoperative recurrent laryngeal nerves palsies were nearly twice as frequent in the AC group compared with the BC group, although the difference was not statistically significant ($P = 0.1523$). These findings are likely due to the technical difficulty of esophagectomy above the carina. The younger mean age of patients in the AC group selected for operation may reflect this more difficult surgical technique.

In patients with carcinoma above the carina and who underwent esophagectomy with 3-field dissection, the rate of lymph node metastasis in the abdomen was lower than those with tumor below the carina, although the rates of metastasis in the neck and mediastinum were similar. A similar finding has been reported in other studies of 3-field lymph node dissection [15,16].

In the TNM classification, thoracic esophageal carcinoma with cervical lymph node metastasis is classified as stage M1, although tumors above the carina are in very close proximity to the cervical lymph nodes. This may account for the satisfactory survival rates of patients with cervical lymph node metastases in comparison with recently published results [17]. Our results suggest that esophagectomy is indicated in patients who have a carcinoma located above the carina that does not involve the adjacent tracheobronchial tree or aorta and without distant organ metastasis, even if there is metastasis in the cervical or mediastinal lymph nodes. The operation should include a cervical and mediastinal lymph node dissection because of the high rates of metastasis in these nodes and the acceptable prognoses after this dissection.

Patients who underwent nonsurgical treatments or incomplete tumor resection had a similar prognosis regardless of the site of the tumor, but the survival was equally poor with any treatment modality and much worse than in those undergoing curative esophagectomy. The larger percentage of patients not deemed appropriate to undergo curative surgery with tumor above the carina compared with those below may be a major reason for their worse prognosis.

Because adjuvant treatments before surgery were performed only for T4 tumors and because postoperative radiotherapy was mostly given for residual tumor in the patients with tumor above the carina, their effects on survival at first sight appears to be poor. However, as the number of patients who underwent preoperative or postoperative adjuvant treatments was small and the selection of treatments was biased, their survival benefit cannot be adequately assessed.

The reason for the lower percentage of female patients with a tumor above the carina is unclear. Epidemiologic investigation is required to resolve this issue, although a larger number of patients will be necessary to do this.

CONCLUSIONS

Curative treatment is not necessarily related only to tumor location, although the prognosis of carcinoma above the carina is generally worse than that of tumors arising below the carina. The poorer prognosis is largely due to the close anatomical relationship of the esophagus with the tracheobronchial tree resulting in lower resectability. When the tumor is found not to have invaded to the adjacent tracheobronchial tree or aorta, however, a radical esophagectomy in skilled hands offers a relatively favorable prognosis. Long-term survival should then be ~45%.

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